CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PYRETHRINS

Chemical Code # 510, Tolerance # 128
SB 950 # 199

January 6, 1987
Revised 5/20/92, 9/3/93, 12/12/95, 2/08/96, 10/08/96

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect[1].
Chronic toxicity, dog:	No data gap, no adverse effect.
Oncogenicity, rat:	No data gap, possible adverse effect[1].
Oncogenicity, mouse:	No data gap, possible adverse effect.
Reproduction, rat:	No data gap, possible adverse effect.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.

Gene mutation: No data gap, no adverse effect.

Chromosome effects: No data gap, no adverse effect.

DNA damage: No data gap, possible adverse effect.

Neurotoxicity: Not required at this time, acceptable study, no adverse effect.

Toxicology one-liners are attached.

1 See note below under Combined, Rat.

All record numbers through 145810 and 956176 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T961008
Revised by S. Morris, 10/8/96.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

****128-505 088856**, "Evaluation of Pyrethrum Extract in a Two Year Dietary Toxicity and Oncogenicity Study in Rats", E.I. Goldenthal, International Research and Development Corporation, Laboratory Project I.D. 556-011, 7/12/90. Pyrethrins (Pyrethrum Extract Task Force Blend # FEK-99, 57.754% state purity) was administered in the feed at concentrations of 0 (control 1), 0 (control 2), 100, 1,000, or 3,000 ppm (corrected for purity, w/w) to 60 Charles River CD* rats / sex / group for 104 weeks. Terminal survival and body weights were comparable for all treatment groups. Non-oncogenic effects were slightly decreased mean body weight gain for the first 78 weeks in both sexes and increased incidence of skin keratoacanthomas in males at 3,000 ppm and increased incidences of accentuated liver lobulation in males at 1,000 and 3,000 ppm (NOEL = 100 ppm). A **possible adverse effect** was indicated by increased incidences of thyroid hyperplasia and follicular cell adenomas in males at 1,000 and both sexes at 3,000 ppm. The study was unacceptable as a combined chronic toxicity/oncogenicity study (J. Kishiyama and S. Morris, 1/3/92) but upgraded to an acceptable onocogenicity study by submission of an adequate rationale for the doses used. The study is not acceptable and not upgradeable as a chronic toxicity study because the high dose did not produce frank toxicity. See note below (S. Morris and J. Gee, 12/19/95).

128-600 118052, "Evaluation of Pyrethrum Extract in a 13-Week Dose Range Finding Study in Rats" E. I. Goldenthal, International Research and Development Corporation, Mattawan, MI, ID # 556-010, 7/22/88. Evaluation of these data and the registrant's comments (DPR doc. # 128-600, letter dated 10/12/92, response dated 10/9/92) resulted in a change in status from "possibly upgradeable" to "not upgradeable" for the study at DPR doc. # 128-505, rec. # 088856 (see DPR Response dated 9/3/93). No worksheet was done (S. Morris, 9/3/93).

128-764 142845: This document contains the U.S.E.P.A.'s evaluation of the study at DPR doc. # 128-505, rec. # 088856. Evalution of this submission did not result in a study status change (S. Morris, see DPR Response dated 12/12/95).

The study status for the rat oncogenicity test type was changed from "data gap, inadequate study, possible adverse effect indicated" to "no data gap, possible adverse effect". The study status for the rat chronic toxicity test type remains "data gap, inadequate study, possible adverse effect indicated". See Worksheet W088856.S01 and Meeting M951115 (S. Morris, 12/19/95).

Note: We have reviewed DPR's data base for Pyrethrins and found the collective data to be adequate at this time to fill the data gap for the rat chronic toxicity test type. The possible adverse oncogenic effect seen in the rat combined study is listed in the data gap status for the rat oncogenicity test type. The combined study was found acceptable to fill the rat oncogenicity data gap in part because of this possible oncogenic effect. Further regulatory evaluations by DPR will be based in part upon these findings.

The no observed effect level (NOEL) for non-oncogenic effects in the rat combined study is 5 mg/kg/day (100 ppm). This is comparable to NOEL's for non-oncogenic effects seen in other acceptable chronic studies: dog chronic toxicity (15 mg/kg/day, 500 ppm), mouse oncogenicity (15 mg/kg/day, 100 ppm), and rat reproduction (5 mg/kg/day, 100 ppm). A replacement study designed to adequately characterizes chronic toxicity in rat would differ little from the present study except the dose levels might be greater. Although the NOEL for rat chronic toxicity might therefore increase, regulatory evaluations would still take into consideration other NOEL's comparable to the present value. Submission of an adequate rat chronic toxicity study will have no foreseeable impact on further regulatory evaluations. At this time, the collective oncogenicity and chronic toxicity data are adequate for foreseen regulatory evaluations by DPR. For this reason submission of an adequate chronic toxicity study is not required at this time. Changes in the "possible adverse effect" data gap status for the rat oncogenicity test type will require submissions of new and adequate chronic toxicity and oncogenicity studies in rat. see DPR Response, 2/8/96 (G. Patterson, J. Gee and S. Morris).

128-787 145809: The registrant submitted comments about DPR's findings. No worksheet was done. See DPR Response dated 10/8/96 (S. Morris 10/8/96).

CHRONIC TOXICITY, RAT

See combined, rat above.

128-040 956001. "Pyrethrins - Pyrethrum: Chronic Toxicity for Higher Animals - Rats Rabbits", McGlaughlin Gormley King Co., Technical Bulletin, December 1966. This document contains a two sentence summary. No worksheet was prepared (J. Kishiyama, 9/26/90).

128-279 956176. Exact duplicate of 128-040 956001, no worksheet (J. Kishiyama, 9/26/90).

CHRONIC TOXICITY, DOG

**128-503 088854, "Evaluation of Pyrethrum Extract in a One Year Chronic Toxicity Study in Dogs", E.I. Goldenthal, International Research and Development Corporation, Laboratory Project I. D. 556-007, 5/18/90. Pyrethrin (Pyrethrum Extract Task Force Blend FEK-99, label #011831-00, stated purity 57.754%) was administered in the feed at concentrations of 0, 100, 500, or 2,500 ppm to 4 beagles/sex/group for 52 weeks. There was no treatment-related effect on mean body weights. Statistically but not biologically significant effects at 2500 ppm were decreased white cell counts and increased serum alanine amino transferase in females and decreased erythrocyte counts and increased liver weights in males (NOEL = 500 ppm). There were no other treatment-related effects. <u>No adverse effect</u> was indicated. The study was unacceptable (S. Morris and J. Kishiyama, 12/16/91) but upgraded by submission of an adequate rationale for the doses used (S. Morris and J. Gee, 8/30/93).

128-602 118054, "Evaluation of Pyrethrum Extract in an Eight-Week Dose Range Finding Toxicity Study in Dogs", International Research and Development Corporation, Mattawan, MI, ID # 556-006, 4/19/88. Evaluation of these data and the registrant's comments about DPR's findings (DPR doc. # 128-600, letter dated 10/12/92, response dated 10/9/92) resulted in a change in study status (see worksheet, S. Morris, 8/30/93).

ONCOGENICITY, RAT

See combined, rat above.

ONCOGENICITY, MOUSE

****128-504 088855**, "Evaluation of Pyrethrum Extract in an Eighteen Month Dietary Oncogenicity Study in Mice", E.I. Goldenthal, International Research and Development Corporation, Laboratory Project I.D. 556-013, 7/5/90. Pyrethrin (Pyrethrum Extract Task Force Blend #FEK-99, label #011831-00, stated purity 57.754%) was administered in the feed at concentrations of 0 (control 1), 0 (control 2), 100, 2,500, or 5,000 ppm to 60 Charles River CD∗-1 mice/sex/group for 18 months. Group mean body weights of the treated groups were always > 95% of controls. Effects reported in both sexes at 2,500 and 5,000 ppm were: increased dark discoloration and vacuolar fatty changes in the liver; statistically significant increases in absolute liver weights and liver/body and liver/brain weight ratios (NOEL = 100 ppm). A **possible adverse effect** was indicated by increased lung nodules and masses in both sexes at 5,000 ppm. The study was unacceptable (S. Morris and J. Kishiyama, 12/27/91) but upgraded by submission of an adequate rationale for the doses used (S. Morris and J. Gee, 9/3/93).

128-600 118051. This document contained the registrant's comments and no additional data. This document did not appear on DPR's Pesticide Registration Data Index printout or the SB-950 Toxicology Summary Spreadsheet. Evaluation of these comments resulted in a

change in status of the study at DPR doc. # 128-504, rec. # 088855 (see DPR worksheet W123116.832, S. Morris, 9/3/93).

128-625 123116; "Evaluation of Pyrethrum Extract in a 13-Week Dose Range Finding Study in Mice", IRDC 556-008, 7/22/88. Evaluation of these data resulted in no change in status of the study at DPR doc. # 128-504, rec. # 088855 (see DPR response dated 9/3/93 and worksheet W123116.832, S. Morris, 9/3/93).

REPRODUCTION, RAT

**** 128-492 086971**, "Two Generation Reproduction Study in Rats with Pyrethrum Extract", J. L. Schardein, International Research and Development Corp., IRDC 556-005, 12/14/89. A reproduction study using Charles River COBS* CD* rats was conducted by dietary exposure to pyrethrins (Pyrethrum Extract Task Force Blend, #FEK-99, 57.574% stated purity) at 0, 100, 1,000, or 3,000 ppm for two generations (F0, F1) with 2 litters / generation (F1a, F1b, F2a, F2b). Twenty-eight adult F0 rats / sex / group were continuously exposed for a minimum of 77 days and then through 2 complete cycles (F1a, F1b) of mating, pregnancy, parturition, and lactation. Twenty-eight F1b offspring / sex / group were possibly exposed in utero from conception through gestation; via mother's milk during weaning; and in the diet for a minimum of 95 days post-weaning, and then through 2 complete cycles (F2a, F2b) of mating, pregnancy, parturition, and lactation. There were no significant treatment-related effects on fertility, fecundity, or pup survival. A **possible adverse effect** was indicated by treatment-related decreases in mean pup birth weights at 3,000 (both sexes, F1a, F2a) and 1,000 ppm (both sexes, F2a) and pup weight gain at 3,000 (both sexes, all litters) and 1,000 ppm (females, F1a, F1b; both sexes, F2a; NOEL = 100 ppm). The decrease in weight gain for F1b's persisted through adulthood. With this exception, there were no significant treatment-related effects on the F0 and F1 adults. The study was acceptable (J. Kishiyama and S. Morris, 11/8/91).

128-600, response dated 10/9/92. This submission contained the registrant's comments and statistical treatment of the data in the study at doc. # 128-492, rec. # 086971.

Evaluation of this submission resulted in no change in study status. No worksheet was done. See DPR Response dated 9/3/93 (S. Morris, 9/3/93).

TERATOLOGY, RAT

**128-494 086975, "Evaluation of Pyrethrum Extract in a Definitive Rat Teratology Study", J.L. Schardein, International Research and Development Corporation, IRDC 556-002, 7/30/87. Pyrethrin (Pyrethrum Extract Task Force Blend #FEK-99, label #011831-00, stated purity 55.574%, 0.5% methylcellulose vehicle) was administered by oral gavage at concentrations (corrected for purity) of 0, 5, 25, or 75 mg/kg/day to 25 mated (gestation day 0) female Sprague-Dawley rats/group on gestation days 6 through 15. There were no treatment-related signs of maternal or developmental toxicity. No adverse effect was indicated (maternal and developmental NOEL's $\geq$ 75 mg/kg/day). The study was unacceptable (S. Morris and J. Kishiyama, 12/13/91) but upgraded to acceptable by submission of an adequate rationale for the doses used (S. Morris and J. Gee, 9/9/93).

128-494 118056, "Range-Finding Teratology Study in Rats with Pyrethrum", IRDC 555-001, 8/26/87. Evaluation of these data and the registrant's comments (DPR doc. # 128-600, letter dated 10/12/92, response dated 10/9/92) resulted in the study at doc. # 128-494, rec. # 086975 being upgraded to acceptable (see worksheet S. Morris, 9/9/93).

TERATOLOGY, RABBIT

**128-494 086976, "Evaluation of Pyrethrum Extract in a Definitive Rabbit Teratology Study", J.L. Schardein, International Research and Development Corporation, IRDC 556-004, 7/22/87. Pyrethrin (Pyrethrum Extract Task Force Blend FEK-99, label #011831-00, stated purity 55.574%, 0.5% methylcellulose vehicle) was given by oral gavage at concentrations of 0, 25, 100, or 250 mg/kg/day to 16 artificially-inseminated New Zealand White SPF female rabbits/group on gestation days 7 through 19. Group mean body weights of the treated does were always > 93% of

controls. Transient behavioral effects were seen after administration of the mid and high doses. One high-dose doe aborted on gestation day 28. No other treatment-related effects on the does or conceptus were reported (maternal NOEL ≥ 250 mg/kg/day, developmental NOEL ≥ 250 mg/kg/day). No adverse effect was indicated. The study was unacceptable (S. Morris and J. Kishiyama, 12/13/91) but upgraded with submission of an adequate rationale for dose selection (S. Morris and J. Gee, 9/3/93).

128-603 118055, "Range-Finding Teratology Study in Rabbits with Pyrethrum Extract", IRDC 556-003, 8/11/87. Evaluation of these data and the registrant's comments (DPR doc. # 128-600, registrant response dated 10/9/92) resulted in a change in status for the study at DPR doc. # 128-494, rec. # 086976 (see worksheet was done, S. Morris, 9/3/93).

GENE MUTATION

** 128-493 086972, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay", R.H.C. San and K. A. Springfield, Microbiological Associates, Inc., Laboratory Study Number T8729.501014, 12/28/89. Pyrethrum Extract (Blend FEK-99, purity 57.55%, w/w) was assayed at 0 (acetone), 292, 585, 877, 2924, 5848, or 8772 µg/plate by the plate incorporation method of measuring mutation rates of the histidine locus of Salmonella typhimurium. Triplicate plates of tester strains TA98, TA100, TA1535, TA1537, and TA1538 were incubated for 48 hours without or with metabolic activation (S-9 fraction of liver homogenates from Aroclor 1254-induced, male Sprague-Dawley rats). Treatment-related increases in mutagenicity or cytotoxicity were not seen. Adequacy of exposure concentrations were demonstrated by precipitation of the test material. The positive controls were adequate. The study was acceptable with no adverse effect indicated (S. Morris and J. Kishiyama, 11/8/91).

CHROMOSOME EFFECTS

128-493 086974, "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells", D. L. Putman and M. J. Morris, Microbiological Associates, Laboratory Study Number T8729.337, 12/28/89. Pyrethrum Extract (Blend FEK-99, purity 57.55%, w/w) was tested for induction of chromosome aberrations in Chinese hamster ovary cells without metabolic activation at nominal concentrations of 0.0, 0.01, 0.02, 0.04, or 0.08 µl/ml or with metabolic activation (S-9 fraction of liver homogenates from Aroclor 1254-induced, male Sprague-Dawley rats) at 0.0, 0.04, 0.08, 0.16, or 0.32 µl/ml (concentrations not corrected for purity, final concentration of DMSO vehicle Z 1%). Exposure to test material (18 hours without activation, 2 hours with) was followed by incubation in fresh media until harvest 20 hours after initiation of exposure. Colcemid was added at 0.1 µg/ml for last 2 hours. A preliminary assay showed cytotoxicity at ≥ 0.0005 µg/ml without activation and ≥ 0.005 µg/ml with activation. The positive controls were adequate. There were no treatment-related increases in chromosome aberrations. No adverse effect was indicated. The study was unacceptable and not upgradeable because the range of exposures in the main assay was too narrow and did not include non-cytotoxic doses and adequate evidence that cells were in M1 at the single harvest time (S. Morris and J. Kishiyama, 11/22/91).

128-768 142924: This document contains registrant's comments about DPR's evaluation of the study at DPR doc. # 128-493, rec. # 086974. Evalution of this submission did not result in a study status change (S. Morris, see DPR Response dated 12/12/95).

128-771 144111: This document contains a protocol for a replacement chromosome aberration study in Chinese hamster ovary cells. See DPR Response, 1/26/96 (J. Gee, 1/26/96).

** 128-788 145810; "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells", Laboratory Study Number G96AC14.330001; P.T. Curry; Microbiological Associates, Inc., Rockville, MD; March 26, 1996. Duplicate cultures of Z 10^6 Chinese hamster ovary cells (CHO-K$_1$) were treated for 6 hours with pyrethrum extract (blend FEK-99, 55.98% stated purity, DMSO vehicle) with or without S9 metabolic activation system (9,000 g supernatant from Aroclor 1254-induced, male Sprague-Dawley rat liver homogenates), washed and reincubated in fresh medium and harvested 12, 24, or 48 hours after initiation of treatment. Colcemid* was added at 0.1 µg/ml for the

last 2 hours. Treatment concentrations (corrected for purity) were: 0, 40, 55, 70, or 85 µg/ml (12 hour harvest, -S9); 0, 25, 40, 55, or 70 µg/ml (12 hour harvest, +S9); 12.5, 25, 50, 100 µg/ml (24 hour harvest, % S9); 6.25, 12.5, 25, or 50 µg/ml (48 hour harvest, -S9); or 0, 40, 55, 70, or 85 µg/ml (48 hour harvest, +S9). Harvested cells were stained, dried, and 100 metaphase cells / duplicate culture were microscopically scored for chromosome aberrations. Treatment levels were adequately justified by a preliminary toxicity study that showed 100% cell growth inhibition at 300 µg/ml % S9. Positive controls were adequate. There were no treatment-related effects on structural chromosome aberrations. An adverse effect was not indicate. The study was acceptable (S. Morris and J. Gee, 9/12/96).

DNA DAMAGE

**** 128-493 086973**, "Unscheduled DNA Synthesis Assay in Rat Primary Hepatocytes with a Confirmatory Assay", R.D. Curren, Microbiological Associates, Inc., Laboratory Study Number T8729.380009, 12/22/89. Pyrethrum Extract (Blend FEK-99, purity 57.55%, w/w) was tested for unscheduled DNA synthesis (UDS) at nominal concentrations of 0.0, 0.03, 0.1, 0.3, 0.6, 1.0, or 3.0 µl/ml (final concentration of acetone vehicle Z 1%). Three plates of primary rat hepatocytes per dose were exposed for 18 to 20 hours in the presence of the test material and [3H]-thymidine. UDS was measured by autoradiographic analysis of [3H]-thymidine incorporated into nuclear DNA (fixed by ethanol-acetic acid). Cytotoxicity was assayed in parallel plates by measuring the per cent of total lactate dehydrogenase activity (LDH) released into the medium. The UDS and cytotoxicity assays were performed twice. The test material was immiscible at ≥ 1.75 µl/ml. Significant LDH release occurred at ≥ 0.3 µl/ml. Positive controls were adequate. A **possible adverse effect** was indicated by a treatment-related increase in mean nuclear grain counts and nuclei with ≥ 5 nuclear grain counts. The study was acceptable (J. Kishiyama and S. Morris, 11/18/91).

NEUROTOXICITY

Not required at this time.

** 128-643 129258 "Acute Oral Neurotoxicity Study with Pyrethrum Extract in Rats", Laboratory Project ID 92N1036; S.J. Hermansky and J.M. Hurley; Bushy Run Research Center, Export, PA; 9/14/93. Fifteen CD* rats/sex/group were treated by single oral gavage with 10% (males) or 5% (females) solutions of pyrethrum extract (Task Force Blend FEK-99, Lot No. LS92-37, 57.5% (w/w), corn oil vehicle) at 0, 0.04, 0.125, or 0.4 g/kg for males and 0, 0.02, 0.063, or 0.2 g/kg for females. Clinical signs were observed twice daily. Functional observational battery (FOB) and motor activity were measured at 3 hours and 7 and 14 days. All surviving animals were sacrificed on day 15 and gross pathology, brain weights, and histologic neuropathology were assessed. Lethalities were 5/15 males at 0.4 g/kg and 2/15 females at 0.2 g/kg. Other treatment related effects in surviving males at 0.4 g/kg and females at 0.2 g/kg were: tremors, urogenital area wetness, salivation, perinasal encrustation, exaggerated startle response, decreased grip strength and hind leg splay, and increased body temperature. Tremors were also seen in 3/15 females at 0.063 g/kg. Fine movement, rears, and ambulation were decreased on day 1 for males at 0.125 and 0.4 g/kg and females at 0.2 g/kg. Male body weights were slightly decreased at 0.4 g/kg. There were no treatment-related gross pathology findings and minimal to moderate neurological findings in 4/15 females at 0.2 g/kg. Male NOEL = 0.04 g/kg and female NOEL = 0.02 g/kg. No adverse was effect indicated. The study was acceptable (S. Morris and J. Gee, 1/11/96).

128-644 129259 "Peroral (Gavage) Neurotoxicity Probe Study with Pyrethrum Extract in CD* Rats", Laboratory Project ID 91N0122; S.J. Hermansky and J.M. Hurley; Bushy Run Research Center, Export, PA; 9/16/93. CD* rats were dosed by single oral gavage with pyrethrum extract (Task Force Blend, Lot No. LS92-37, corn oil vehicle). In phase I, one rat/sex/group was dosed with a 25% (males) or 10% (females) solution at 0.2, 0.4, 0.8, 1.4 or 2.5 g/kg for males or 0.05, 0.1, 0.2, 0.4, or 0.8 g/kg for females. Tremors were seen in males at 0.2, 0.4, 0.8, 1.4 or 2.5 g/kg and females at 0.05, 0.1, 0.2, 0.4, or 0.8 g/kg. Males at 1.4 and 2.5 g/kg and females at 0.2, 0.4 and 0.8 g/kg died after lying on stomachs, labored respiration, salivation, urine stains, and prostration. In phase II, 2 to 4 rats/sex/group were dosed with 10% (males), 2.5% (females), or 5%

(females) solutions at 0.0, 0.04, 0.1, 0.2, or 0.4 g/kg for males or 0.0, 0.025, 0.05, 0.1, 0.15, 0.2 g/kg for females. There were no mortalities. Effects in males were: tremors, piloerection, perinasal encrustation and red extremities at 0.4 g/kg and decreased level of arousal at 0.1, 0.2, or 0.4 g/kg. Effects in female were: tremors at 0.1, 0.15, and 0.2 g/kg, altered gait at 0.15g/kg, and perinasal encrustation and hyperactivity at 0.2 g/kg. These data were adequate to justify the doses used in the study at DPR doc. # 128-643, rec. # 129258. No worksheet was done (Morris, 1/11/96).

The following documents were reviewed for this Summary of Toxicology Data:

128-040 043428 (missing from volume, probably 128-040 956001)
128-279 045011 (missing from volume, probably 128-279 956176)
128-492 086971
128-493 086972
128-493 086973
128-493 086974
128-494 086975
128-494 086976
128-503 088854
128-504 088855
128-505 088856
128-600 118051 (not on printout)
128-600 118052
128-600 118054
128-603 118055
128-604 118057
128-625 123116
128-643 129258
128-764 142845
128-768 142924
128-771 144111
128-787 145809
128-788 145810
128-040 956001 (not on printout)
128-279 956176 (not on printout)

This document was not in the volume or on the printout.

128-604 118057

The following documents were on the printout for pyrethrins but contained studies that used piperonyl butoxide as the test material and were not reviewed:

127-002 038479 (missing from volume, probably 127-002 907616)
127-008 038479 (missing from volume, probably 127-008 068066)
127-002 038480 (missing from volume, probably 127-002 907616)
127-008 038480 (missing from volume, probably 127-008 068066)
127-002 038481 (missing from volume, probably 127-002 907616)
127-008 038481 (missing from volume, probably 127-008 068066)
128-351 039789 (not on printout)
128-351 039791 (missing from volume, probably 128-351 039789)
128-279 045010
128-293 045014 (duplicate of 128-351 039789)
127-008 068066 (duplicate of 127-002 907616)
127-002 907616 (not on printout)